

amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 495-535 of a wild-type HBV polymerase.

56. (New) An isolated HBV mutant, comprising a mutation in the gene encoding the HBV DNA polymerase resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type HBV, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-535 of a wild-type HBV polymerase.

57. (New) An isolated HBV mutant, comprising a mutation in the gene encoding the HBV DNA polymerase resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type HBV, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-529 of a wild-type HBV polymerase.

F ⁴ 58. (New) An isolated HBV mutant exhibiting, relative to an isolated wild-type HBV, reduced sensitivity to a nucleoside analogue and reduced interactivity to an antibody to a wild-type HBV surface antigen, said HBV mutant comprising at least one of:

- (i) a nucleotide sequence of its genome as set forth in SEQ ID NO:17 or a sequence having at least 60% similarity thereto;
- (ii) a nucleotide sequence capable of hybridising to SEQ ID NO:17 under low stringency conditions at 42°C;
- (iii) a mutation in an overlapping portion of open reading frames for DNA polymerase and HBV surface antigen; and
- (iv) a mutation in a region corresponding to amino acids 118 to 169 and/or 169 to 207 of HBV surface antigen,

wherein said mutant contains a Trp/Arg499Glu amino acid substitution in the DNA

polymerase and an Asp144Glu and Gly145Arg amino acid substitution in the surface antigen.

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59. (New) The isolated HBV mutant according to any of claims ~~55~~ or ~~58~~ wherein said nucleoside analogue is selected from the group consisting of famciclovir, penciclovir and lamivudine.

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60. (New) The HBV mutant according to any of claims 55 or 58 wherein said at least one amino acid substitution is selected from the group consisting of Arg/Trp499Glu, Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Thr530Ser, and Ile533Leu.

61. (New) The HBV mutant according to claim 59 wherein said at least one amino acid substitution is selected from the group consisting of Arg/Trp499Glu, Phe512Leu, Val519Leu, Pro523Leu, Leu526Met, Thr530Ser, and Ile533Leu.

62. (New) An isolated HBV mutant exhibiting, relative to an isolated wild-type HBV, reduced sensitivity to a nucleoside analogue, said mutant comprising at least one mutation in its genome wherein said at least one mutation produces at least one amino acid substitution in the DNA polymerase selected from the group consisting of Trp/Arg499Glu, Phe512Leu and Val519Leu, said amino acid substitution in the DNA polymerase resulting in a concurrent amino acid substitution in the overlapping open reading frame of the HBV surface antigen.

63. (New) An isolated HBV mutant exhibiting, relative to an isolated wild-type HBV, reduced sensitivity to a nucleoside analogue, said mutant comprising at least one mutation in its genome wherein said at least one mutation produces at least one amino acid substitution in the DNA polymerase selected from the group consisting of Trp/Arg499Glu, Phe512Leu, Val519Leu and Ser559Thr, said amino acid substitution in

the DNA polymerase resulting in a concurrent amino acid substitution in the overlapping open reading frame of the HBV surface antigen.

64. (New) An isolated mutant according to claim ~~62~~ or ~~63~~, wherein said nucleoside analogue is selected from the group consisting of famciclovir, penciclovir and lamivudine.

65. (New) A method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding the B domain of HBV polymerase corresponding to amino acid residues 495-535 of a wild-type HBV polymerase, with said mutation resulting in at least one amino acid substitution, deletion and/or addition in said B domain,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of lamivudine, penciclovir and famciclovir.

66. (New) A method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding the B domain of HBV polymerase corresponding to amino acid residues 505-535 of a wild-type HBV polymerase, with said mutation resulting in at least one amino acid substitution, deletion and/or addition in said B domain,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of lamivudine, penciclovir and famciclovir.

87. ¹³ (New) A method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding the B domain of HBV polymerase corresponding to amino acid residues 505-529 of a wild-type HBV polymerase, with said mutation resulting in at least one amino acid substitution, deletion and/or addition in said B domain,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of lamivudine, penciclovir and famciclovir.

FI 68. ¹⁴ (New) A method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding HBV DNA polymerase, wherein the screening detects at least one mutation selected from the group consisting of Arg/Trp499Glu, Phe512Leu, Val 519Leu, Pro523Leu, Leu526Met, Thr530Ser, Ile533Leu, Met550Val and Met550Ile,

such that when said at least one amino substitution in the DNA polymerase is Met550Val or Met550Ile, said method detects at least one amino acid substitution other than Phe512Leu, Leu526Met or Val553Ile,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of lamivudine, penciclovir and famciclovir.

69. ¹⁵ A method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of penciclovir and famciclovir, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in a nucleotide sequence encoding HBV DNA polymerase,

wherein the screening detects at least one mutation selected from the group consisting of Arg/Trp499Glu, Phe512Leu, Val 519Leu, Pro523Leu, Leu526Met, Thr530Ser, Ile533Leu, Met550Val and Met550Ile,

wherein the presence of such a mutation is an indication of the potential of reduced sensitivity of said HBV to at least one of penciclovir and famciclovir.

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70. (New) The method according to any of claims ~~11~~, ~~14~~ or ~~15~~, wherein the screening for a mutation comprises sequencing said isolated HBV DNA or corresponding mRNA.

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71. (New) The method according to any of claims ~~11~~, ~~14~~ or ~~15~~, wherein the screening for a mutation comprises a PCR method or PCR-based method.

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72. (New) The method according to any of claims ~~11~~, ~~14~~ or ~~15~~, wherein the screening for a mutation comprises a hybridization method.

73. (New) A method for screening the antiviral potential of anti-HBV agents against HBV mutants which have decreased sensitivity to a nucleoside analogue relative to an isolated wild-type HBV, said method comprising measuring the lethal dose of said agents against said mutants.

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74. (New) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 495-535 of a wild-type HBV polymerase.

75. (New) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside